

# PARAMETER IDENTIFIABILITY OF ARTEMISININ SYNTHESIS USING DESIGN OF EXPERIMENTS

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## ABSTRACT

Artemisinin-based combination therapies are recommended by the World Health Organization to treat malaria, one of the most abundant infectious diseases in the world. Recently, a novel production route, which combines the extraction and the catalyzed chemical synthesis, has been shown to be a promising sustainable processing alternative [Triemer, 2018]. To exploit its mechanism, operational settings and limits, mathematical modeling might be beneficial when thorough system insight is required. In a first step, we consider the catalyzed synthesis step from dihydroartemisinic acid to artemisinin, and we show that only a subset of the parameters of the considered model is identifiable with the available sparse data using a singular value decomposition approach. In a second step, within the framework of design of experiments (DoE), we demonstrate the effect of additional experimental data to overcome the non-identifiability problem of the model parameters.

*Keywords: parameter identifiability, design of experiments, parameter sensitivities, singular value decomposition, antimalarial artemisinin synthesis*

## INTRODUCTION

In the case of antimalarial drugs, artemisinin is an essential precursor to several active pharmaceutical ingredients (APIs). Aiming for lower costs, the two-step partial synthesis of dihydroartemisinic acid (DHAA) to artemisinin has gained interest in academia and industry. To improve the production of artemisinin, process systems engineering concepts can be applied. For instance, mathematical process models may predict the best catalysts, solvents, reaction conditions, as well as the overall reactor type and operating conditions. However, when applying model-based process design concepts, the risk of false predictions and misinterpretations depends critically on data quality and uncertainties of the identified model parameters, respectively. Besides a valid process model and informative experimental data, the model parameters have to be theoretically identifiable. In the literature, various identifiability concepts exist, but only some of these methods apply to complex, non-linear process models. In this study, we determine the local parameter sensitivity matrix for a simplified process model of the two-step partial synthesis of DHAA to

artemisinin, and we analyze the parameter identifiability of this process model using a singular value decomposition approach [Stigter, 2017]. To improve the parameter identifiability, we also apply a model-based design of experiments (DoE) concept that demonstrates the effect of additional experimental data on the parameter identifiability.

## METHODS

Frequently, dynamic processes are described via ordinary or partial differential equation systems, and the model parameters  $p$  are identified via numerical optimization methods minimizing the differences between simulation results and experimental data. The parameter identification problem, however, might be ill-posed in the case of non-identifiable model parameters. In DoE and the identifiability analysis, the local parameter sensitivity matrix is an essential measure [Schenkendorf, 2018] and is defined as:

$$SM_{t_k}[i, j] = \left. \frac{\partial y_i}{\partial p_j} \right|_{t_k},$$

where  $y_i$  is the  $i$ th model response function and  $p_j$  the  $j$ th model parameter. If the sensitivity matrix  $SM$  is singular, that is, the matrix is rank deficient, the model parameters cannot be identified properly [Stigter, 2017]. To test the rank of the  $SM$ , the singular value decomposition can be used:

$$SM(t_0, \dots, t_k, p) = u_1 \sigma_1 v_1^T + \dots + u_q \sigma_q v_q^T,$$

where  $\sigma_i$  are the singular values,  $u_i$  are the left-singular vectors, and  $v_i$  are the right-singular vectors. Here, zero singular values indicate a lack of identifiability, and the non-zero elements of the corresponding singular vectors  $v_i$  reveal the non-identifiable parameter or parameter combinations.

## RESULTS

The details of the implemented two-phase process model of the partial synthesis of artemisinin, which has 10 system states and 7 unknown model parameters, can be found in [Triemer, 2016]. Moreover, we assumed that 7 of the 10 system states are measurable. In Fig. 1, the resulting singular values are shown. The singular values  $\sigma_i, i \in \{5, 6, 7\}$  are close to zero, that is, the model parameters are non-identifiable. The related singular vectors  $v_i, i \in \{5, 6, 7\}$  clearly show that only a minor subset  $\{p_3, p_6\}$  of the model parameters can be identified in principle; see Fig. 2. In turn, the model parameters  $\{p_4, p_5\}$  and the combination of  $p_1, p_2$ , and  $p_7$  are non-identifiable.

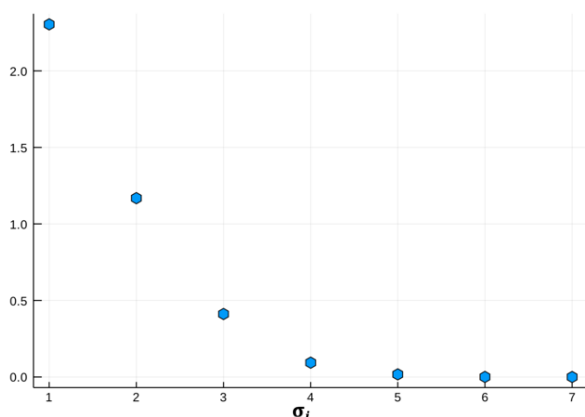


Figure 1: Singular values of the local sensitivity matrix.

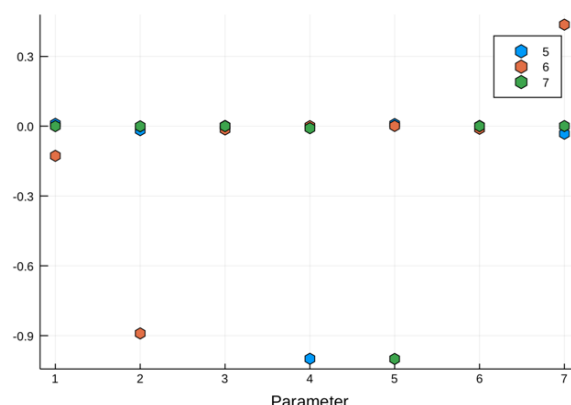


Figure 2: Elements of the right-singular vectors of the singular values  $\sigma_i, i \in \{5, 6, 7\}$ .

When applying DoE and increasing the number of experimental data, we observed no improvement regarding the identifiability. Thus, there is a structural lack of parameter identifiability of the studied process model of the partial synthesis of artemisinin.

## CONCLUSIONS

We studied the identifiability of a given process model of the partial synthesis of artemisinin. Based on the sensitivity matrix and its singular values, we proved that the model parameters are non-identifiable and that additional experimental data do not result in a proper parameter identification problem. Future work will combine DoE and model reduction techniques to improve the parameter identifiability, leading to reliable model-based process analysis and design results for an optimal artemisinin synthesis.

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